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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/893,348	06/28/2001	Michal Eisenbach-Schwartz	EIS-SCHWARTZ-2A	1155

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BROWDY AND NEIMARK, P.L.L.C.
624 NINTH STREET, NW
SUITE 300
WASHINGTON, DC 20001-5303

EXAMINER
BUNNER, BRIDGET E

ART UNIT	PAPER NUMBER
1647	4

DATE MAILED: 09/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/893,348	EISENBACH-SCHWARTZ ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45-60* is/are pending in the application.

4a) Of the above claim(s) *46-48,51,52,54-56,59 and 60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45,49,50,53,57 and 58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *45-60* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *09/314,161* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 30 June 2003 (Paper No. 14) has been entered in full. Claims 1-44 are cancelled and claims 45-60 are added.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Newly submitted claims 46-48, 51-52, 54-56, and 59-60 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The claims are basically drawn to a method of causing activated T cells to accumulate at the site of neuronal degeneration by administering an effective amount of a NS-specific antigen or an effective amount of T cells. The newly submitted claims also recite that an individual is suffering from a disease that has neurodegenerative effects. However, the elected invention recites the administration of a peptide derived from a NS-specific antigen and injury (not disease) was elected as a species (04 November 2002, Paper No. 10).

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 46-48, 51-52, 54-56, and 59-60 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Applicant's continued traversal of the Restriction requirement set forth in Paper No. 9 (02 October 2002) appears moot since the restriction requirement was made final in the previous

Office Action (Paper No. 11, 30 January 2003). If Applicant wishes to pursue the matter further, a petition should be filed in accordance with 37 CFR 1.144.

Claims 45, 49-50, 53, and 57-58 are under consideration in the instant application as they read upon the elected invention of administering a peptide derived from an NS-specific antigen (Paper No. 10, 04 November 2002) and the elected species of injury, central nervous system, spinal cord injury, Nogo-A, and subcutaneously.

Withdrawn Objections and/or Rejections

1. The objections to the specification at pg 4 of the previous Office Action (Paper No. 11, 30 January 2003) are *withdrawn in part* in view of the amended Brief Description of Drawings and title (Paper No. 14, 30 June 2003). Please see section on Specification, below.

2. The objection to claims 1-2, 31, and 41 at pg 4 of the previous Office Action (Paper No. 11, 30 January 2003) is *withdrawn* in view of the cancelled claims (Paper No. 14, 30 June 2003).

3. The rejections to claims 1-2, 31-32, 38-39, and 41 under 35 U.S.C. 112, second paragraph, as set forth at pg 10-11 of the previous Office Action (Paper No. 11, 30 January 2003) are *withdrawn* in view of the cancelled claims (Paper No. 14, 30 June 2003).

4. The supplemental information disclosure statement filed on 15 January 2003 (Paper No. 12) has been considered.

Oath/Declaration

5. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c). The basis for this objection is set forth at pg 4 of the previous Office Action (Paper No. 11, 30 January 2003). Applicant indicates at pg 15-16 of the Response of 30 June 2003 (Paper No. 14) that an application data sheet is attached which corrects the inventor information. However, no such application data sheet was found attached to the Response.

Specification

6. The disclosure is objected to because of the following informalities:

7. Patent applications are referenced in the disclosure (pg 5, lines 17-18; pg 58, linc 11). The status of the applications must be updated. The basis for this objection is set forth at pg 4 of the previous Office Action (Paper No. 11, 30 January 2003). The serial numbers at pages 1 and 5 are still pending. This objection will be maintained until the status of those applications changes or the instant application is deemed allowable.

Double Patenting

8. The rejection of new claims 45, 49-50, 53, and 57-58 rejected under the judicially created doctrine of obviousness-type double patenting as set forth for claims 1, 31-32, and 41 at pg 5-6 of the previous Office Action (Paper No. 11, 30 January 2003) is maintained and held in abeyance until all other issues are resolved. However, Applicant is encouraged to submit a terminal disclaimer at Applicant's earliest convenience.

New Double Patenting

9. Claims 45 and 53 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 38 of copending Application No. 09/314,161. Although the conflicting claims are not identical, they are not

patentably distinct from each other. The claims of the '161 application and the instant application recite a method of causing T cells activated against a NS-specific antigen to accumulate at the site of neuronal degeneration in an individual in need. The recitation of reducing neuronal degeneration caused by neurodegenerative effects of disease, ameliorating the effects of an injury or disease that causes neuronal degeneration, and reducing neuronal degeneration in the central nervous system or peripheral nervous system in the preamble of the claims from the instant application and the '161 application is interpreted as an intended use and bears no accorded patentable weight. Therefore, the instant claims of a method of causing T cells activated against a NS-specific antigen to accumulate at the site of neuronal degeneration is not patentably distinct over the co-pending claim in Application No. 09/314,161.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

10. Claims 45, 49-50, 53, and 57-58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for promoting recovery from spinal cord injury comprising subcutaneously administering to an individual in need thereof a composition comprising a peptide derived from Nogo-A, as set forth in SEQ ID NO: 19, and wherein said composition promotes recovery from spinal cord injury, does not reasonably provide enablement for a method for reducing neuronal degeneration caused by the neurodegenerative effects of disease, or for reducing secondary neuronal degeneration that follows the primary neuronal damage of an injury, in the central or peripheral nervous system of an individual in need thereof, comprising: causing T cells activated against a NS-specific antigen

to accumulate at the site of neuronal degeneration in the individual in need, thereby reducing neuronal degeneration at that site. The specification is also not enabling for a method for ameliorating the effects of an injury or disease that causes neuronal degeneration of the central or peripheral nervous system of an individual in need thereof, comprising causing T cells activated against a NS-specific antigen to accumulate at the site of neuronal degeneration in the individual in need, thereby ameliorating the effects of the injury or disease at that site. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims also recite that the individual in need is one suffering from an injury that has caused primary neuronal damage.

Applicant's arguments (Paper No. 14, 30 June 2003), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant indicates that Prof. Schwartz made a comprehensive presentation (interview of 26 June 2003) explaining why predictions made in the present specification have been proved to be accurate. Applicant asserts that so many embodiments of the specification have been successfully tested that it would no longer be unexpected that the full scope of the present invention would work as disclosed. Applicant contends that it would not take undue experimentation to make and use the invention with respect to other NS-specific peptides or other neurodegenerative diseases or injuries.

Applicant's arguments have been fully considered but are not found to be persuasive. Undue experimentation would still be required of the skilled artisan to determine what other NS-specific antigens and in the instant case, what peptides derived from NS-specific antigens,

could be used to activate T cells and reduce neuronal degeneration, secondary neuronal degeneration, or ameliorate the effects of an injury or disease that causes neuronal degeneration. Relevant literature teaches that about 200,000 distinct mRNA sequences are thought to be expressed in the brain alone (a component of the central nervous system) and that this diversity results from the greater number and variety of cell types in the brain as compared to cells in the more homogeneous body tissues (pg 49, ¶ 1; Schwartz, J., "Synthesis and Trafficking of Neuronal Proteins", Principles of Neural Science, Connecticut: Appleton and Lange, 1991, pages 49-65). Schwartz states that the three membrane systems which constitute separate compartments within the neuron are made up of different proteins and serve separate functions within the cell (pg 50). Schwartz also continues to explain that a nerve cell makes three general classes of proteins: cystolic, nuclear/mitochondrial/peroxisomal, and cell membrane/secretory (pg 50-55). Therefore, due to the large quantity of proteins/antigens present in the central nervous system alone, the present invention is also unpredictable and complex wherein one skilled in the art may not necessarily reduce any kind of neuronal degeneration in the central nervous system or ameliorate the effects of injury or disease that causes neuronal degeneration comprising administering all peptides derived from all possible NS-specific antigens. Since the specification also provides no guidance regarding what type of analogs of the NS-specific antigen and analogs and derivatives of the peptide should be utilized for the desired activity, the skilled artisan must resort to trial and error experimentation to determine which class of compounds might yield one with the desired activity. Again, the Examiner has interpreted the administration of Nogo-A p472 (SEQ ID NO: 19) to be a critical feature of the claimed method since relevant literature teaches that other Nogo-A derived peptides possess growth-cone-

collapsing activity and inhibit neurite outgrowth (for example, GrandPre et al. Nature 403: 439-444, 2000; see pg 442, Figures 4-5). Also, the specification teaches that pre-immunized (p472) SPD male and female rats are subjected to severe spinal cord contusion and a 10-g rod is dropped onto the laminectomized cord (pg 93, lines 19-23). The specification discloses that the rats are immunized subcutaneously with Nogo p472 peptide emulsified in CFA containing *Mycobacterium tuberculosis* while control rats are injected with PBS emulsified in CFA (pg 93, line 24 through pg 94, lines 1-14). The specification teaches that hind limb motor skills of the animals are scored since a therapeutic approach aiming at reducing the spread of damage through neuroprotection will result in better recovery in terms of hind limb motor activity (pg 94, lines 21-24 through pg 95, line 1). Furthermore, the specification teaches that male and female p472-immunized rats significantly improve in overall functional recovery compared to control rats (pg 95, lines 5-17; Figures 24A-B, Figure 25).

However, the specification of the instant application fails to provide any guidance for the successful treatment of any injury, disorder, or disease other than spinal cord injury using the claimed method. The scope of claims 45, 49-50, 53, and 57-58 encompass a method of reducing neuronal degeneration caused by the neurodegenerative effects of disease, a method for reducing secondary neuronal degeneration that follows the primary neuronal damage of an injury, and a method for ameliorating the effects of an injury or disease that causes neuronal degeneration of the central or peripheral nervous system of an individual. The scope encompasses diseases and injuries not expected to be commensurate with the elected species of spinal cord injury, such as Alzheimer's disease, Huntington's disease, prion diseases, stroke, surgery, etc. (pg 44, ¶ 2). The effects encompassed by these diseases are broad and may include for example, memory loss,

cognitive deficits, behavioral changes, and dementia, which effects are not commensurate with spinal cord injury. The etiology and pathology of spinal cord injury is largely dissimilar from other diseases and injuries (particularly of the CNS) and the skilled artisan would not be able to predict that administration of Nogo-A p472 would be beneficial for all possible diseases and injuries. The skilled artisan would also not be able to predict that administration of Nogo-A p472 would cause NS-specific T cells to accumulate at the site of neuronal degeneration.

It is also noted that a broad, reasonable interpretation of the claims encompasses such diseases and injuries as Alzheimer's disease, Parkinson's disease, and Huntington's disease, among others, which have proven to be recalcitrant to treatment in the art (see for example, Halliday et al., Clin Exp Pharmacol Physiol 27: 1-8, 2000; Steece-Collier et al., Proc Natl Acad Sci USA 99(22): 13972-13974, 2002; Feigin et al. Curr Opin Neurol 15: 483-489, 2002).

Specifically, the specification does not teach any methods or working examples that indicate a reduction or amelioration of "primary" neuronal degeneration caused or exacerbated by injury or disease in CNS by administration of Nogo-A p472 to an individual. The specification teaches that "a catastrophic consequence of central nervous system injury is that the primary damage is often compounded by the gradual secondary loss of adjacent neurons that apparently were undamaged, or only marginally damaged by the initial injury"(pg 4, [0008]). The specification also discloses that "neurons in the central nervous system do not undergo spontaneous regeneration following an injury" (pg 5, [0009]). As echoed by Jackowski, it is well known in this unpredictable art that regeneration does not occur in the CNS either because processes fail to grow the necessary distance, they are in competition with other nearby neuronal processes not derived from the affected nerve, astrocytic scarring blocks axonal elongation, or

because of misdirected axonal growth (e.g., see Jackowski, Brit J Neurosurgery 9: 303-317, 1995; specifically pgs. 309-310 and pg. 305, last ¶). Accordingly, because of the lack of guidance provided by the specification as to how one can rescue dead or dying cells instantaneously affected, for example, by a head injury or neurodegenerative disease, there is no nexus that merely administering a peptide derived from Nogo-A to an individual in need thereof can reasonably be extrapolated to successfully treat any human subject experiencing *"primary"* neuronal degeneration, as claimed, without undue experimentation to determine such. The examples in the specification of the instant application only indicate that administration of a peptide derived from Nogo-A, as set forth in SEQ ID NO: 19, promotes recovery from spinal cord injury.

Relevant literature teaches that damage to the CNS is severe and irreversible, in part because of the failure of central neurons to regenerate axons (Kandel et al., Principles of Neural Science. 1991. Connecticut: Appleton and Lange; pg 264-265). Schwab et al. also indicate that "tissue damage and functional losses after spinal cord lesion result from the initial injury, which is immediate and irreversible, and from the reactive cascade of subsequent secondary molecular and cellular processes" (Physiol Rev 76(2): 319-370, 1996; see pg 327, col 2). Schwab et al. also teach that the cascade of secondary processes is reflected in the sequence of pathological changes that take place at the lesion site within days to weeks and that are fairly independent of the nature of the primary injury (see pg 327, col 2). Therefore, one skilled in the art would not expect an inhibition of secondary degeneration to also treat primary degeneration because the art indicates the primary "insult" or degeneration is irreversible and the processes involved in secondary degeneration are separate from those of the primary injury.

(ii) Applicant indicates that there are numerous references which relate to the present invention and reviews the results of several of them. Applicant argues that these papers establish for the record what Prof. Schwartz was able to explain at the interview of 26 June 2003. Applicant submits that in light of all the experiments that have been done with respect to this invention, the full scope of the present would be expected to be operable. Applicant asserts that there is no reason to believe that undue experimentation would be involved in order to make and use the full scope of the present invention.

Applicant's arguments have been fully considered but are not found to be persuasive. Any references which the Applicant wishes for the Examiner to review and make of record should be supplied in the form of an Information Disclosure Statement pursuant to 37 C.F.R. § 1.98(a)(1) which requires a list of all patents, publications, or other information submitted for consideration by the Office. The list of references has been placed in the application file, but the information referred to therein has not been considered. Submission of the proper PTO-1449 form with copies of the references listed therein will be taken into due consideration by the Examiner. It is noted that the Examiner has previously considered a few of the references listed in the response of 30 June 2003 (Paper No. 14; for example, Moalem et al. (Nat Med 5(1): 49-55, 1999), Hauben et al. (PNAS USA 98: 15173-15178, 2001, Hauben et al. J. Neurosci 20: 6421-6430, 2000). However, only the elected invention is being examined at this time. Until the elected invention is deemed allowable, the references are not pertinent. The references will be considered when allowable subject matter relevant to the elected invention is identified.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to prevent neuronal degeneration in an individual and to generate peptides to all possible NS-specific antigens and administer each of these peptides to an individual, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the unpredictability of the effects of the administration of all possible peptides derived from NS-specific antigens in an individual, and the breadth of the claims which fail to recite any structural limitations about a specific peptide derived from an NS-specific antigen, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

Elizabeth C Kemmerer

BEB
Art Unit 1647
12 September 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER